



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM12/0131

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APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/578,656	05/25/00	015	NGUYEN, Q	1632 01/31/01
First Named Applicant	LI, 35 USC 154(b) term ext. = 0 Days.			

TITLE OF INVENTION: KNOCKOUT-TRANSGENIC MOUSE MODEL OF SPINAL MUSCULAR ATROPHY

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 4910-3	800-009.000	B45	UTILITY	NO	\$1240.00	04/30/01

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

Notice of Allowability

Application No.

09/578,656

Examiner

Quang Nguyen, Ph.D.

Applicant(s)

LI ET AL.

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☐ This communication is responsive to _____.
2. ☒ The allowed claim(s) is/are 1, 20-23 and 25-34.
3. ☐ The drawings filed on _____ are acceptable as formal drawings.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) ☐ All b) ☐ Some* c) ☐ None of the:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- * Certified copies not received: _____.
5. ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE FOR SUBMITTING NEW FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION.** This three-month period for complying with the REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL is extendable under 37 CFR 1.136(a).

6. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
7. ☐ Applicant MUST submit NEW FORMAL DRAWINGS
 - (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review(PTO-948) attached
 - 1) ☐ hereto or 2) ☐ to Paper No. _____.
 - (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the examiner.
 - (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

8. ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any reply to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE / SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

- | | |
|--|---|
| 1 <input type="checkbox"/> Notice of References Cited (PTO-892) | 2 <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3 <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 4 <input checked="" type="checkbox"/> Interview Summary (PTO-413), Paper No. <u>8</u> . |
| 5 <input checked="" type="checkbox"/> Information Disclosure Statements (PTO-1449), Paper No. <u>6</u> . | 6 <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 7 <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit of Biological Material | 8 <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9 <input type="checkbox"/> Other |

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Kent Cheng on January 25, 2001.

The application has been amended as follows:

The Claims:

Claims 18 and 19 have been cancelled because they are drawn to the non-elected invention. Claim 24 has been cancelled and it is replaced by a new claim 34.

Claims 1, 20-23 and 25-33 have been rewritten as follows:

e¹
Claim 1. A transgenic mouse whose genome comprises a homozygous disruption of an *Smn* gene such that said *Smn* gene does not produce functional Smn protein, wherein the mouse's genome additionally comprises a DNA sequence encoding human SMN protein, wherein expression of said DNA sequence encoding human SMN protein makes said mouse viable, said mouse showing one or more neurological defects similar to the pathological features of an SMN patient.

e²
Claim 20. The transgenic mouse of claim 1, wherein said homozygous disruption in said *Smn* gene is a knockout mutation and said DNA sequence contains a copy of human SMN^c gene.

Art Unit: 1632

Claim ~~21~~³. The transgenic mouse of claim ~~20~~², wherein said knockout mutation comprises an insertion in said mouse *Smn* gene of a hypoxanthine phosphoribosyl-transferase cassette.

Claim ~~22~~⁴. The transgenic mouse of claim ~~21~~³, wherein said hypoxanthine phosphoribosyl-transferase cassette is inserted in exon 7 of said mouse *Smn* gene.

Claim ~~23~~⁵. The transgenic mouse of claim ~~20~~², wherein said knockout mutation comprises a replacement of exon 7 of said mouse *Smn* gene by a hypoxanthine phosphoribosyl-transferase cassette.

Claim ~~25~~⁷. The method of claim ~~34~~⁶, wherein said disruption is a knockout mutation.

Claim ~~26~~⁸. The method of claim ~~25~~⁷, wherein said knockout mutation is introduced by inserting in said mouse *Smn* a hypoxanthine phosphoribosyl-transferase cassette or by replacing exon 7 of said mouse *Smn* with a hypoxanthine phosphoribosyl-transferase cassette.

Claim ~~27~~⁹. The method of claim ~~26~~⁸, wherein said human genomic DNA sequence further comprises a copy of centromeric *SERF1* and a portion of centromeric *NAIP*.

Claim ~~28~~¹⁰. A method of testing for therapeutic efficacy of an agent on one or more symptoms of spinal muscular atrophy, said method comprising:

- ² (a) applying one or more agents to be tested to a transgenic mouse of claim ~~20~~²; and
- (b) determining whether one or more symptoms of spinal muscular atrophy have changed as a result of application of said agent or agents.

¹¹
Claim ~~29~~ The method of claim ~~28~~¹⁰, wherein said agent corrects genetic defects by changing one or more genomic DNA sequences of said transgenic mouse.

¹²
Claim ~~30~~ The method of claim ~~28~~¹⁰, wherein said agent is a chemical compound which alleviates one or more symptoms of spinal muscular atrophy.

¹³
Claim ~~31~~ The method of claim ~~28~~¹⁰, wherein said transgenic mouse is made according to claim ~~28~~⁵.

¹⁴
Claim ~~32~~ The method of claim ~~31~~¹³, wherein said agent corrects genetic defects by changing one or more genomic DNA sequences of said transgenic mouse.

¹⁵
Claim ~~33~~ The method of claim ~~31~~¹³, wherein said agent is a chemical compound which alleviates one or more symptoms of spinal muscular atrophy.

¹⁶
Claim ~~34~~ A method of generating a transgenic mouse having a symptom of spinal muscular atrophy, comprising the steps of:

(a) generating a first line of mouse that has a heterozygous disruption for a mouse *Smn* locus (*Smn*^{+/-});

(b) generating a second line of mouse whose genome possesses a human genomic DNA sequence having a copy of human SMN^c gene;

(c) crossing a mouse of said second line with a mouse of said first line to obtain a third line of mouse with a genotype of *Smn*^{+/-} SMN^c; and

(d) crossing a mouse of said third line with a mouse of said first line or intercrossing among mice of said third line to obtain a transgenic mouse having a symptom of spinal muscular atrophy, bearing a genotype of *Smn*^{+/-} SMN^c.

Art Unit: 1632

REASONS FOR ALLOWANCE:

The following is an examiner's statement of reasons for allowance: The amendments to the claims have overcome the rejection of record. The prior art of record does not teach or fairly suggests the generation of a transgenic mouse of the instant invention, a method of making the same and a method of testing for therapeutic efficacy of an agent using the same transgenic mouse, especially in view of the unpredictability for generating transgenic animals with expected phenotypes.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Deborah Crouch, Ph.D., may be reached at (703) 308-1126, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Quang Nguyen, Ph.D.
Art Unit 1632

Karen M. Hauda
KAREN M. HAUDA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

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ATTACHMENT TO AND MODIFICATION OF
NOTICE OF ALLOWABILITY (PTO-37)
(November, 2000)

NO EXTENSIONS OF TIME ARE PERMITTED TO FILE CORRECTED OR FORMAL DRAWINGS, OR A SUBSTITUTE OATH OR DECLARATION, notwithstanding any indication to the contrary in the attached Notice of Allowability (PTO-37).

If the following language appears on the attached Notice of Allowability, the portion lined through below is of no force and effect and is to be ignored¹:

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE **THREE MONTHS** FROM THE "DATE MAILED" of this Office action. Failure to comply will result in ABANDONMENT of this application. ~~Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).~~

Similar language appearing in any attachments to the Notice of Allowability, such as in an Examiner's Amendment/Comment or in a Notice of Draftperson's Patent Drawing Review, PTO-948, is also to be ignored.

¹ The language which is crossed out is contrary to amended 37 CFR 1.85(c) and 1.136. See "Changes to Implement the Patent Business Goals", 65 Fed. Reg. 54603, 54629, 54641, 54670, 54674 (September 8, 2000), 1238 Off. Gaz. Pat. Office 77, 99, 110, 135, 139 (September 19, 2000).

a